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ORIGINAL PAPER

The impact of pharmaceutical innovation on premature cancer mortality in Switzerland, 1995–2012

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Abstract The premature cancer mortality rate has been declining in Switzerland, but there has been considerable variation in the rate of decline across cancer sites (e.g., breast or digestive organs). I analyze the effect that pharmaceutical innovation had on premature cancer mortality in Switzerland during the period 1995–2012 by investigating whether the cancer sites that experienced more pharmaceutical innovation had larger declines in premature mortality, controlling for the number of people diagnosed and mean age at diagnosis. Premature cancer mortality before ages 75 and 65 is significantly inversely related to the cumulative number of drugs registered 5, 10, and 15 years earlier. The number of drugs registered during 1980–1997 explains 63 % of the variation across cancer sites in the 1995–2012 log change in the premature (before age 75) mortality rate. Controlling for the cumulative number of drugs, the cumulative number of chemical subgroups does not have a statistically significant effect on premature mortality. This suggests that drugs (chemical substances) within the same class (chemical subgroup) are not "therapeutically equivalent". Over 17,000 life-years before age 75 were gained in 2012 due to drugs registered during 1990–2007. The number of life-years before age 75 gained in 2012 from drugs registered during two earlier periods (1985–2002 and 1980–1997) were more than twice as great. Since mean utilization of new drugs is much lower than mean utilization of older drugs, more recent drug registrations may have a smaller effect on premature mortality than earlier drug registrations even if the average quality of newer drugs is higher. Estimates of the cost per life-year gained before ages 75 and 65 in 2012 from drugs registered during 1990–2007 are $21,228 and $28,673, respectively. These figures are below even the lowest estimates from the value-of-life literature of the value of a quality-adjusted life-year. The estimates indicate that the cost per life-year before age 75 gained from drugs registered during earlier periods (1985–2002 and 1980–1997) were considerably lower: $5299 and $3218, respectively. The largest reductions in premature mortality occur at least a decade after drugs are registered, when their utilization increases significantly. This suggests that if Switzerland is to obtain substantial additional reductions in premature cancer mortality in the future (a decade or more from now) at a modest cost, pharmaceutical innovation (registration of new drugs) is needed today.

Keywords Mortality · Longevity · Cancer · Neoplasm · Pharmaceutical · Innovation · Chemotherapy

JEL Classification I10 · J11 · L65 · O33 · O47

Introduction

Previous authors have argued that "reducing premature mortality is a crucial public health objective" [16]. A widely used measure of premature mortality is years of potential life lost (YPLL) before a given age (e.g., age 70), i.e., the number of years not lived by an individual who died before that age [1]. Statistics of YPLL are published by the World Health Organization, the OECD, and government agencies of the U.S., Switzerland, and other countries. Burnet et al. [2] argue that YPLL "should be considered when allocating research funds".

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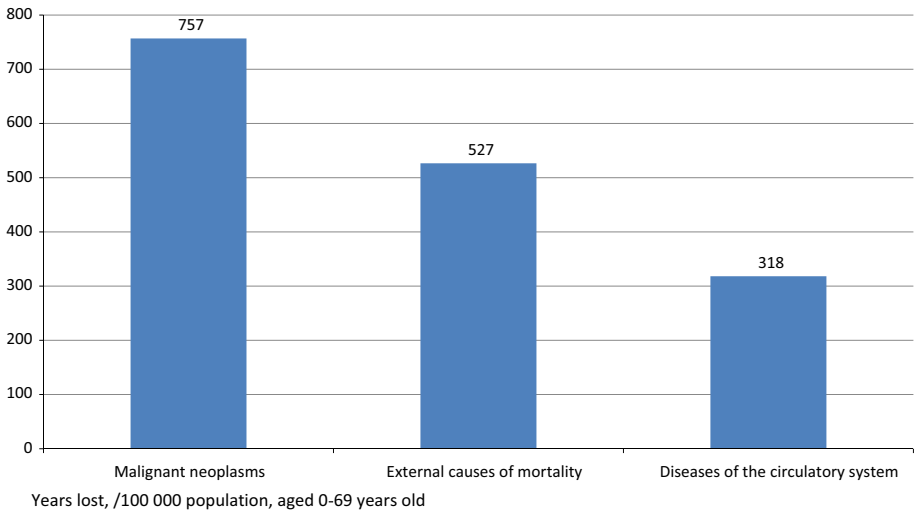

Fig. 1 Premature (before age 70) mortality rates from three largest causes, Switzerland 2010

As shown in Fig. 1, in Switzerland in 2010, cancer (malignant neoplasms) was the largest cause of premature mortality: the number of years of potential life lost before age 70 (YPLL70) due to cancer was 44 % larger than YPLL70 due to external causes and 138 % larger than YPLL70 due to diseases of the circulatory system. However, as shown in Fig. 2, the premature cancer mortality rate has been declining; it declined about 27 % between 1995 and 2010. The cancer incidence rate remained approximately constant during that period.

While the premature mortality rate from all cancers combined has been declining in Switzerland, Fig. 3 indicates that there has been considerable variation in the rate of decline across cancer sites. During the period 1995–2012, premature (before age 75) mortality from cancer of lymphoid, hematopoietic, and related tissue declined 31 %, and from breast cancer declined 38 %, but premature mortality from lip, oral cavity, and pharynx cancer increased 14 %, and from cancer of endocrine glands and related structures increased 19 %. This variation in the rate of decline of premature mortality cannot be explained by variation in the rate of decline of incidence.

In this paper, I will analyze the effect that pharmaceutical innovation has had on premature cancer mortality in Switzerland during the period 1995–2012.[1] As shown in Fig. 4, the number of drugs used to treat cancer that had ever been launched in Switzerland increased almost fivefold between 1980 and 2010; the number of "cancer drugs" (antineoplastic and immunomodulating agents) used to treat cancer increased almost sixfold.

The analysis will be performed using fixed-effects and long-differences research designs (see McKinnish [12]) based on longitudinal disease-level data. In essence, I will investigate whether the cancer sites that experienced more pharmaceutical innovation had larger declines in the premature mortality rate, controlling for changes in the incidence rate. Figure 5 illustrates that the rate of pharmaceutical innovation, as measured by the number of drugs launched during the period 1986–2011, varied considerably across cancer sites. Twenty-nine drugs were launched for breast cancer, while only 15 or 16 drugs were launched for each of three other types of cancer: connective and soft tissue, male genital organs, and female genital organs.

The analysis will be based on aggregate data—longitudinal data on 13 cancer sites[2]—rather than patient-level data. Stukel et al. [20] argue that comparisons of outcomes between patients treated and untreated in observational studies may be biased due to differences in patient prognosis between groups, often because of unobserved treatment selection biases. I believe that difference-in-differences estimates based on aggregate panel data are much less likely to be subject to unobserved treatment selection biases than estimates based on cross-sectional patient-level data.[3] Moreover, the outcome measures that I

[1] Lichtenberg [10] analyzed the impact of pharmaceutical innovation and other types of medical innovation on cancer mortality in the US during the period 2000–2009. However, as the Commonwealth Fund [3] demonstrated, the US Health Care System differs dramatically from the health care systems of other OECD countries, including Switzerland. For example, in 2008, per-capita spending on health was 63 % higher in the US than it was in Switzerland. In 2012, per-capita expenditure on pharmaceuticals was 80 % higher in the US than it was in Switzerland.

[2] The 13 cancer sites are the malignant neoplasm ICD-10 blocks defined by the World Health Organization [21].

[3] Jalan and Ravallion [7] argued that "aggregation to village level may well reduce measurement error or household-specific selection bias" (p. 10).

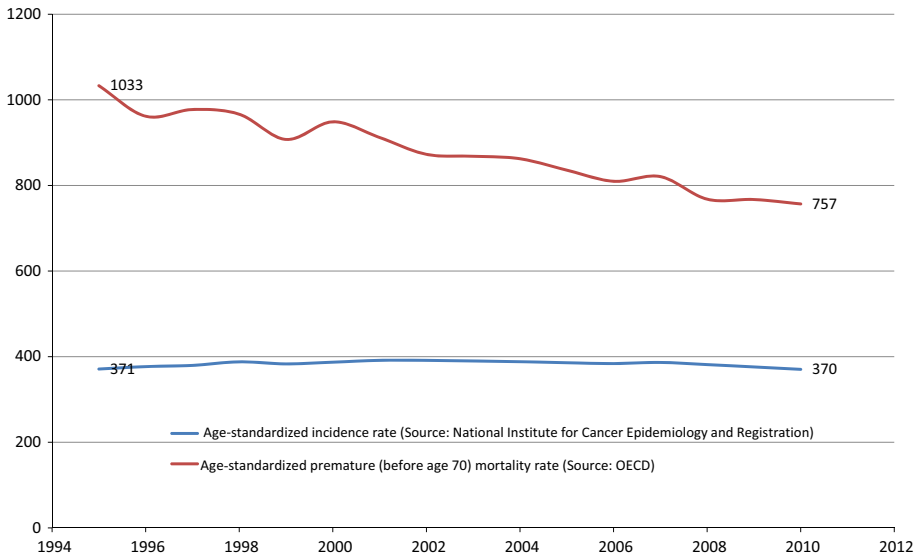

Fig. 2 Cancer incidence rate and premature (before age 70) cancer mortality rate, Switzerland 1995–2010

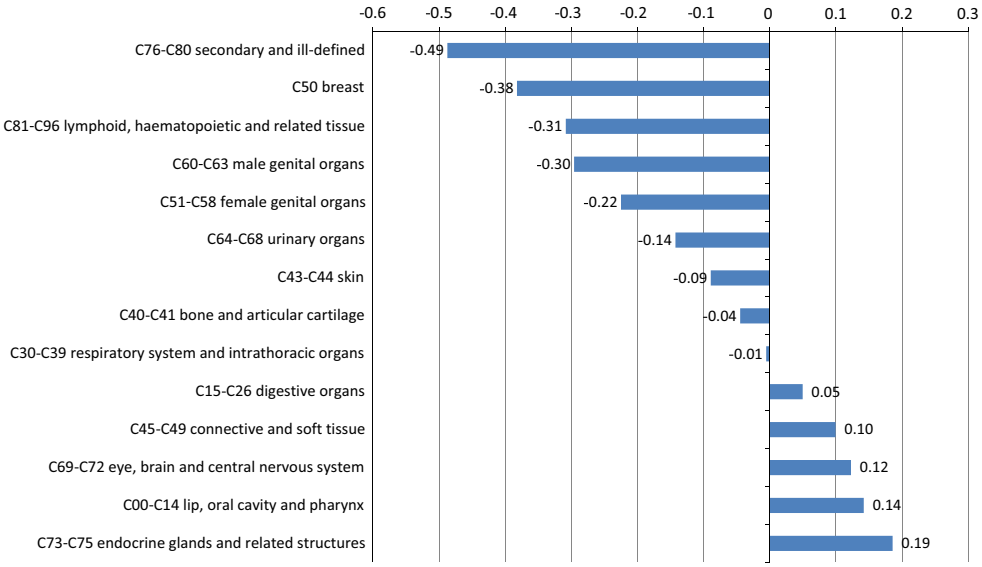

Fig. 3 Log change in years of potential life lost before age 75, by type of cancer, Switzerland, 1995–2012

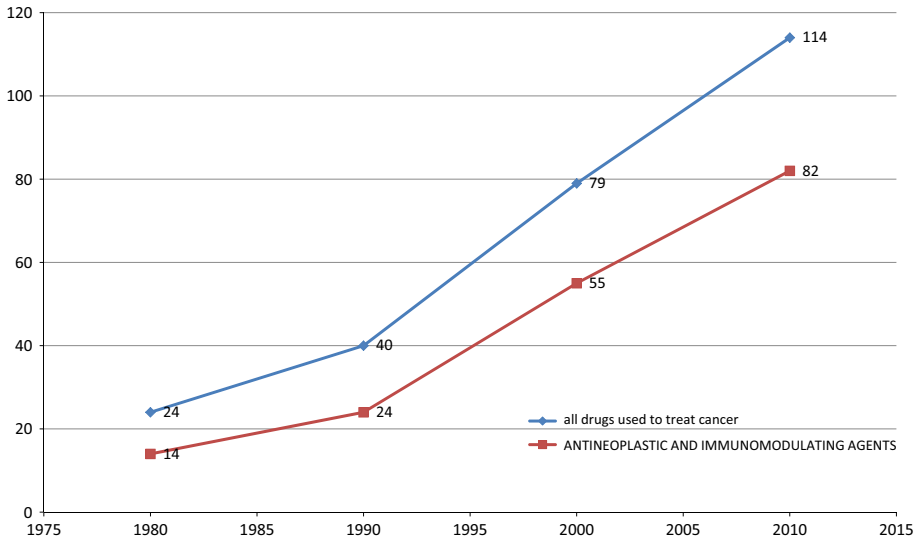

Fig. 4 Number of drugs used to treat cancer ever launched in Switzerland, 1980–2010

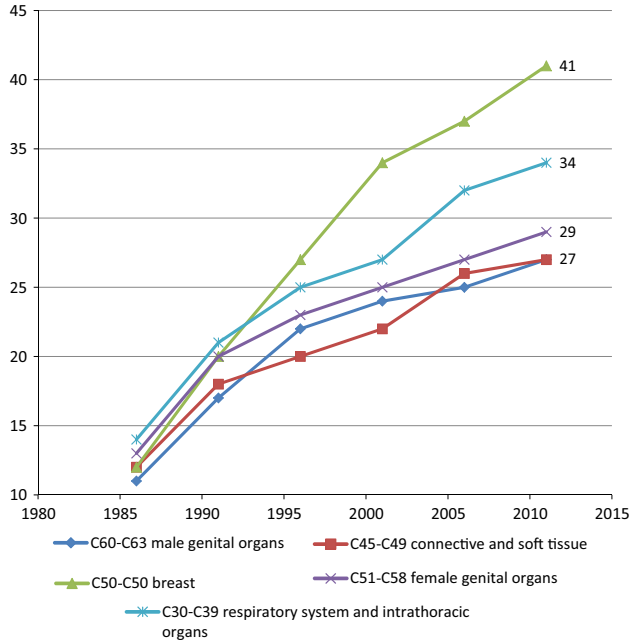

Fig. 5 Number of drugs that had been launched in Switzerland for treating five types of cancer, 5-year intervals, 1986–2011

analyze (premature mortality rates) are not subject to lead-time bias.[4]

In "Premature cancer mortality model ", I describe an econometric model of premature cancer mortality. The data sources used to construct the data to estimate this model are described in "Data". Empirical results are presented in "Empirical results". Key implications of the estimates are discussed in "Discussion". "Summary and conclusions" provides a summary and conclusions.

Premature cancer mortality model

In his model of endogenous technological change, Romer [17] hypothesized an aggregate production function such that an economy's output depends on the "stock of ideas" that have previously been developed, as well as on the economy's endowments of labor and capital. The premature mortality model that I will estimate may be considered a health production function, in which premature mortality is an inverse indicator of health output or outcomes, and the cumulative number of drugs approved is analogous to the stock of ideas. The first model will be of the following form:

$$\ln(\text{YPLL75}_{s,t}) = \beta_k \text{CUM\_NCE}_{s,t-k} + \gamma \ln(\text{CASES\_LT75}_{s,t-1}) + \pi \text{AGE\_DIAG}_{s,t-1} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (1)$$

where

$\text{YPLL75}_{s,t}$	= years of potential life lost before age 75 from cancer at site s per 100,000 people below age 75 in year t (t = 1995, … , 2012)
$\text{CUM\_NCE}_{s,t-k}$	= $\sum_d \text{IND}_{ds}\ \text{REGISTERED}_{d,t-k}$ = the number of new chemical entities (drugs) to treat cancer at site s that had been registered in Switzerland by the end of year $t - k$
IND_{ds}	= 1 if drug d is used to treat (indicated for) cancer at site s
	= 0 if drug d is not used to treat (indicated for) cancer at site s
$\text{REGISTERED}_{d,t-k}$	= 1 if drug d was registered in Switzerland by the end of year $t - k$
	= 0 if drug d was not registered in Switzerland by the end of year $t - k$
$\text{CASES\_LT75}_{s,t-1}$	= the number of new cases of cancer at site s diagnosed in people below age 75 per 100,000 people below age 75 in year $t - 1$
$\text{AGE\_DIAG}_{s,t-1}$	= the mean age at which people who were diagnosed with cancer at site s in year $t - 1$ were diagnosed
α_s	= a fixed effect for cancer at site s
δ_t	= a fixed effect for year t

The most recent available incidence data are for the year 2011

Inclusion of year and cancer-site fixed-effects controls for the overall decline in premature cancer mortality and for stable between-disease differences in premature mortality.[5] A negative and significant estimate of β_k in Eq. (1) would signify that diseases for which there was more pharmaceutical innovation had larger declines in premature mortality. $\beta_k \times (\text{CUM\_NCE.}_{,2012-k} - \text{CUM\_NCE.}_{,1995-k})$, where $\text{CUM\_NCE.}_{,t-k}$ is the mean of $\text{CUM\_NCE}_{s,t-k}$, is an estimate of the decline in Swiss premature cancer mortality during the sample period (1995–2012) that can be attributed to the introduction of new drugs. The functional form of Eq. (1) has the property of diminishing marginal productivity: the absolute reduction in premature mortality declines with each successive increase in the number of drugs.

[4] Survival time for cancer patients is usually measured from the day the cancer is diagnosed until the day they die. Patients are often diagnosed after they have signs and symptoms of cancer. If a screening test leads to a diagnosis before a patient has any symptoms, the patient's survival time is increased because the date of diagnosis is earlier. This increase in survival time makes it seem as though screened patients are living longer when that may not be happening. This is called lead-time bias. It could be that the only reason the survival time appears to be longer is that the date of diagnosis is earlier for the screened patients, but the screened patients may die at the same time they would have without the screening test. See (National Cancer Institute [13]).

[5] The year fixed effects also control for population growth.

As illustrated by Fig. 6, the data exhibit heteroskedasticity: cancer sites with larger total premature mortality during 1995–2012 had smaller (positive and negative) annual percentage fluctuations in YPLL75. Equation (1) will therefore be estimated by weighted least-squares, weighting by the mean premature mortality rate during 1995–2012 ($(\Sigma_t\ \mathrm{YPLL75}_{s,t})/18$). The standard errors of Eq. (1) will be clustered within cancer sites.

Although one would expect an increase in true cancer incidence to increase premature cancer mortality, cancer incidence rates are subject to measurement error, so one should not necessarily expect the coefficient on measured cancer incidence (γ) to be positive. Let I and I^* represent measured and true cancer incidence, respectively. Then $I = (I/I^*) \times I^*$, and $\log(I) = \log(I/I^*) + \log(I^*)$. Measured cancer incidence can increase for two reasons: an increase in true cancer incidence, or an increase in the ratio of measured incidence to true incidence. The latter could occur as a result of increasing quantity or quality of cancer screening. More and better cancer screening could lead to earlier diagnosis, which might reduce premature mortality. Therefore the effect on premature mortality of increases in I^* and increases in (I/I^*) may offset one another: the former is likely to increase premature mortality, but the latter may reduce it. For this reason, although controlling (in an unrestrictive manner) for measured incidence in the premature mortality model seems appropriate, we should not be surprised if we don't find a significant effect of measured incidence on premature mortality.

Equation (1) also includes mean age at time of diagnosis (AGE_DIAG) as an explanatory variable. Like the number of cases diagnosed, mean age at time of diagnosis could change for two reasons. First, the true mean age of onset of the disease could change; a reduction in the true mean age of onset would be likely to increase premature mortality. Second, the lag from time of onset to time of diagnosis could change; a reduction in this lag, which would reduce mean age at time of diagnosis, would be likely to reduce premature mortality. Hence, the sign of the coefficient (π) on $\mathrm{AGE\_DIAG}_{s,t-1}$ in Eq. (1) is ambiguous, a priori. Nevertheless, it seems desirable to control for mean age at time of diagnosis in the premature mortality equation.[6]

The measure of pharmaceutical innovation in Eq. (1)—the number of chemical substances previously commercialized to treat a disease—is not the theoretically ideal measure. Premature mortality is presumably more strongly related to the drugs actually used to treat a disease than it is to the drugs that could be used to treat the disease. A preferable measure is the mean vintage of drugs used to treat cancer at site s in year t, defined as $\mathrm{VINTAGE}_{st} = \sum_d Q_{dst}\mathrm{LAUNCH\_YEAR}_d / \sum_d Q_{dst}$, where Q_{dst} = the quantity of drug d used to treat cancer at site s in year t, and $\mathrm{LAUNCH\_YEAR}_d$ = the world launch year of drug d.[7] Unfortunately, measurement of $\mathrm{VINTAGE}_{st}$ is infeasible: even though data on the total quantity of each drug in each year ($Q_{d.t} = \Sigma_s\ Q_{dst}$) are available, many drugs are used to treat multiple diseases,[8] and there is no way to determine the quantity of drug d *used to treat cancer at site s in year t*.[9] However, Lichtenberg [9] showed that in France, there is a highly significant positive correlation across drug classes between changes in the (quantity-weighted) vintage of drugs and changes in the number of chemical substances previously commercialized within the drug class.

Pharmaceutical innovation is not the only type of medical innovation that is likely to reduce premature mortality. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect premature mortality. Therefore, measures of these other types of medical innovation should be included in the Eq. (1). Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation are not available for Switzerland. However, failure to control for non-pharmaceutical medical innovation is unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for two reasons. First, more than half of US funding for biomedical research came from pharmaceutical and biotechnology firms [4]. Much of the rest came from the

[6] Controlling for the distribution of people diagnosed by cancer stage (local, regional, distant) might also be desirable, although due to the phenomenon of 'stage migration' [5], measured changes in the stage distribution may be due to improvements in diagnostic imaging—metastases that had formerly been silent and unidentified are now identified—rather than a true change in the disease distribution. Consistent with that phenomenon, in an analysis of US data, Lichtenberg (2014) found no relationship across cancer sites between the change in the stage distribution and the change in the age-adjusted mortality rate. Data on the number of people diagnosed by cancer site, stage, and year are not available for Switzerland.

[7] According to the Merriam Webster dictionary, one definition of vintage is "a period of origin or manufacture (e.g., a piano of 1845 vintage)". http://www.merriam-webster.com/dictionary/vintage. Solow [19] introduced the concept of vintage into economic analysis. Solow's basic idea was that technical progress is "built into" machines and other goods and that this must be taken into account when making empirical measurements of their roles in production. This was one of the contributions to the theory of economic growth that the Royal Swedish Academy of Sciences cited when it awarded Solow the 1987 Alfred Nobel Memorial Prize in Economic Sciences [15].

[8] For example, dactinomycin is used to treat C45–C49 connective and soft tissue neoplasms, C51–C58 female genital organ neoplasms, C60–C63 male genital organ neoplasms, and C64–C68 urinary organ neoplasms.

[9] Outpatient prescription drug claims usually don't show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g., chemotherapy) often show the indication of the drug, but these account for just 15 % of drug expenditure. These data are not available for Switzerland.

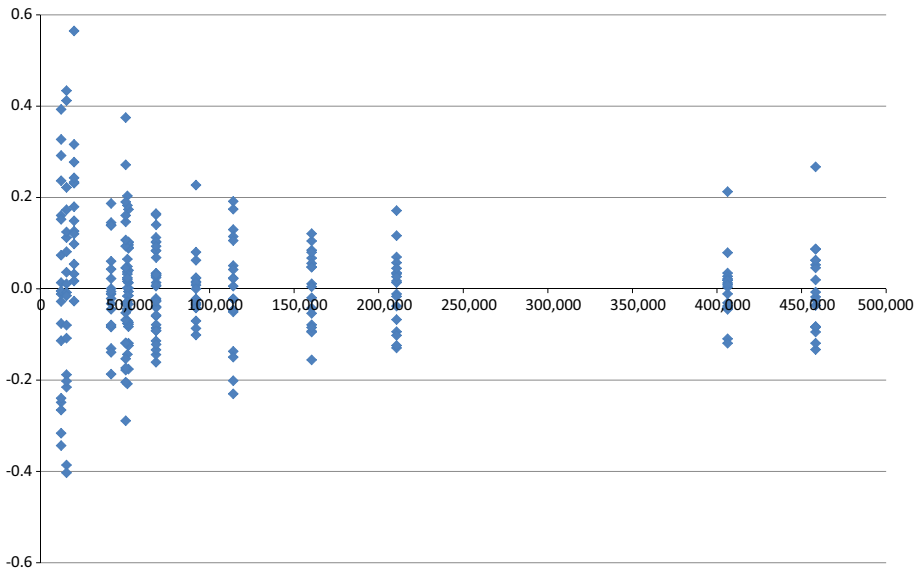

Fig. 6 Plot of the residuals from the (unweighted) regression $\ln(\text{YPLL75st}) = \alpha s + \delta t + \varepsilon st$ against total premature (before age 75) mortality during 1995–2012 (Σt YPLL75st)

federal government (i.e., the NIH), and new drugs often build on upstream government research [18]. The National Cancer Institute [14] says that it "has played an active role in the development of drugs for cancer treatment for 50 years… [and] that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed" at the National Cancer Institute.

Second, previous research based on US data indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. Lichtenberg [9] showed that, in the US during the period 1997–2007, the rate of pharmaceutical innovation was not positively correlated across diseases with the rate of medical procedure innovation and may have been negatively correlated with the rate of diagnostic imaging innovation. Also, Lichtenberg [10] found that estimates of the effect of pharmaceutical innovation on US cancer mortality rates were insensitive to the inclusion or exclusion of measures of non-pharmaceutical medical innovation. This suggests that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth.

In Eq. (1), premature mortality from cancer at site s in year t depends on the number of new chemical entities (drugs) to treat cancer at site s launched in Switzerland by the end of year $t - k$, i.e., there is a lag of k years. Eq. (1) will be estimated for different values of k: $k = 0, 5, 10, 15, 20, 25, 30$.[10] One would expect there to be a substantial lag because new drugs diffuse gradually—they won't be used widely until years after commercialization. Figure 7 shows data on the mean number of standard units[11] of cancer drugs sold (in thousands) in Switzerland in 2012, by period of launch in Switzerland. Mean utilization in 2012 of drugs launched after 2000 is only 19 % as high as mean utilization of drugs launched during 1951–1990, and 11 % as high as mean utilization of drugs launched during 1991–2000.

The effect of a drug's launch on premature mortality is likely to depend on both the quality and the quantity of the drug. Indeed, it is likely to depend on the interaction between quality and quantity: a quality improvement will have a greater impact on mortality if drug utilization (quantity) is high. Although newer drugs tend to be of higher quality than older drugs (see [11]), the relative quantity of very new drugs is quite low, so the impact on mortality of very new drugs is lower than the impact of older drugs.

Premature mortality in year t presumably depends more on the number of drugs actually used to treat patients in year t ($\text{N\_NCE\_TREAT}_{s,t}$) than it does on the number of drugs registered by year t (or $t - k$). (Some drugs are not used until several years after registration.) $\text{CUM\_NCE}_{s,t-k}$ might be considered a "noisy indicator" of $\text{N\_NCE\_TREAT}_{s,t}$. In other words, $\text{CUM\_NCE}_{s,t-k}$ is

[10] A separate model is estimated for each value of k, rather than including multiple values ($\text{CUM\_NCE}_{i,t-1}$, $\text{CUM\_NCE}_{i,t-2}$, $\text{CUM\_NCE}_{i,t-3}$,…) in a single model because CUM_NCE is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included.).

[11] The number of standard 'dose' units sold is determined by taking the number of counting units sold divided by the standard unit factor which is the smallest common dose of a product form as defined by IMS HEALTH. For example, for oral solid forms the standard unit factor is one tablet or capsule whereas for syrup forms the standard unit factor is one teaspoon (5 ml) and injectable forms it is one ampoule or vial. Other measures of quantity, such as the number of patients using the drug, prescriptions for the drug, or defined daily doses of the drug, are not available.

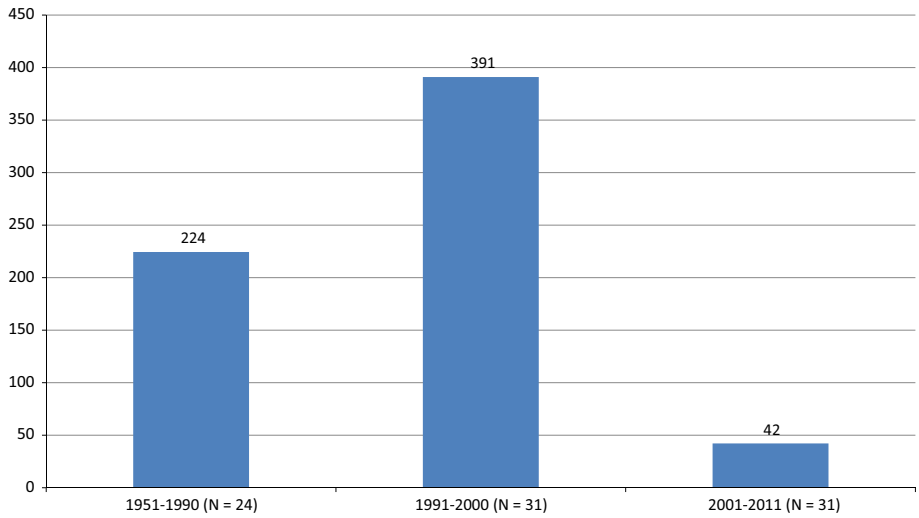

Fig. 7 Mean quantity (000s of standard units) of cancer molecules sold in Switzerland in 2012, by year of launch of molecule in Switzerland

subject to measurement error. Measurement error often biases coefficients towards zero. McKinnish [12] argued that when explanatory variables in panel data models are subject to measurement error, long-difference estimates may be less downward biased than fixed-effects estimates,[12] and that "it seems prudent for researchers to estimate both fixed-effects and long-differences models whenever feasible". Therefore, in addition to estimating the fixed-effects model of the level of premature mortality (Eq. 1) using annual data, I will estimate a long-difference model that can be derived from Eq. (1). A special case of Eq. (1), when $t = 2012$ (the final year of the sample period) and incidence and mean age at diagnosis are excluded (for simplicity) is:

$$\ln\left(\text{YPLL75}_{s,2012}\right) = \beta_k \text{CUM\_NCE}_{s,2012-k} + \alpha_s + \delta_{2012} + \varepsilon_{s,2012} \quad (2)$$

When $t = 1995$ (the initial year of the sample period) and incidence and mean age at diagnosis are excluded:

$$\ln\left(\text{YPLL75}_{s,1995}\right) = \beta_k \text{CUM\_NCE}_{s,1995-k} + \alpha_s + \delta_{1995} + \varepsilon_{s,1995} \quad (3)$$

Subtracting (3) from (2) yields a simple linear regression:

$$\ln\left(\text{YPLL75}_{s,2012}\right) - \ln\left(\text{YPLL75}_{s,1995}\right) = \beta_k\left(\text{CUM\_NCE}_{s,2012-k} - \text{CUM\_NCE}_{s,1995-k}\right) + \left(\delta_{2012} - \delta_{1995}\right) + \left(\varepsilon_{s,2012} - \varepsilon_{s,1995}\right) \quad (4)$$

It is quite plausible that $(\text{CUM\_NCE}_{s,2012-k} - \text{CUM\_NCE}_{s,1995-k})$ is subject to less measurement error than $\text{CUM\_NCE}_{s,t-k}$: the long-run (12-years) change in the number of drugs used to treat a condition can be measured more reliably than the number of drugs used to treat a condition in a particular year.

The measure of pharmaceutical innovation, $\text{CUM\_NCE}_{s,t-k} = \sum_d \text{IND}_{ds}\ \text{LAUNCH}_{d,t-k}$, is based on whether drug d had an indication for cancer at site s *at the end of 2011*. One would prefer to base the measure on whether drug d had an indication for cancer at site s at the end of year $t - k$. FDA data indicate that about one in four new molecular entities has supplemental indications, i.e., indications approved after the drug was initially launched.[13]

In Eq. (1), the measure of premature mortality is the number of years of potential life lost before age 75. To assess the robustness of my results, I will estimate models similar to Eq. (1), using the age threshold 65 as well as 75.

Chemical substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. In the anatomical therapeutic chemical (ATC) classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology, drugs are classified in groups at five different levels. The highest (1st) level is the "anatomical main group" level; there are 14 anatomical main groups. The 2nd, 3rd, 4th, and 5th levels are "therapeutic subgroup", "pharmacological subgroup", "chemical

[12] She provides (in her Table 4) an empirical example in which the magnitude of the 7-year long-difference estimate is more than three times the magnitude of the fixed-effects estimate.

[13] Source: Drugs@FDA Data Files.

subgroup", and "chemical substance", respectively.[14] Premature mortality from a disease may depend on the number of chemical (or pharmacological) subgroups that have previously been developed to treat the disease rather than, or in addition to, the number of chemical substances (drugs) that have previously been developed to treat the disease. This will be investigated by estimating versions of Eq. (4) in which ($CUM\_SUBGROUP_{s,2012-k} - CUM\_SUBGROUP_{s,1995-k}$) is included in addition to or instead of ($CUM\_NCE_{s,2012-k} - CUM\_NCE_{s,1995-k}$), where

$CUM\_SUBGROUP_{s,t-k}$	$= \sum_g IND\_SUBGROUP_{gs} REGISTERED\_SUBGROUP_{g,t-k}$
$IND\_SUBGROUP_{gs}$	= 1 if any drugs in chemical subgroup g are used to treat (indicated for) cancer at site s
	= 0 if no drugs in chemical subgroup g are used to treat (indicated for) cancer at site s
$REGISTERED\_SUBGROUP_{g,t-k}$	= 1 if any drugs in chemical subgroup g had been registered in Switzerland by the end of year $t-k$
	= 0 if no drugs in chemical subgroup g had been registered in Switzerland by the end of year $t-k$

Data

NCE registrations in Switzerland (registered)

Data on new chemical entities registered in Switzerland were constructed from the expanded list of preparations of human and veterinary medicines published by the Swiss Agency for Therapeutic Products. This list includes WHO ATC codes and Swiss registration dates of pharmaceutical preparations.

Drug indications (IND)

Data on drug indications were obtained from Thériaque, a database of official, regulatory, and bibliographic information on all drugs available in France,[15] intended for health professionals. This database is produced by the Centre National Hospitalier d'Information sur le Médicament. In this database, drugs are coded according to WHO ATC codes, and diseases are coded according to WHO ICD-10 codes.[16]

Appendix Table 3 shows drugs (sorted by Swiss launch year) used to treat various types of cancer in Switzerland.

Premature mortality data (YPLL75, YPLL65)

Data on years of potential life lost before ages 75 and 65, by cancer site and year (1995–2012), were constructed from data provided by the Federal Statistics Office.[17]

Cancer incidence data

Data on the number of new cancer cases, by cancer site, age, and year, were obtained from the National Institute for Cancer Epidemiology and Registration.[18] This source also enabled calculation of the mean age of people diagnosed with cancer, by cancer site and year.

Appendix Table 4 shows data on the number of years of potential life lost and the number of new cases diagnosed (in the previous year) before ages 75 and 65, by cancer site, in 1995 and 2012.

Empirical results

Estimates of CUM_NCE coefficients from fixed-effects (FE) and long-difference (LD) models of premature cancer mortality are presented in Table 1. All models controlled for cancer incidence and mean age at diagnosis in the previous year. Controlling for these variables had little effect on estimates of the CUM_NCE coefficients; to conserve space, coefficients on cancer incidence and mean age at diagnosis are not shown in Table 1.

The estimates in the top part of the table (lines 1–3) are of models in which the age threshold for measuring premature mortality is age 75. The estimates in the bottom part

[14] For example, the five levels associated with the chemical subgroup "nitrogen mustard analogues" are:

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01A	Alkylating agents
L01AA	Nitrogen mustard analogues
L01AA01	Cyclophosphamide
L01AA02	Chlorambucil
L01AA03	Melphalan
L01AA05	Chlormethine
L01AA06	Ifosfamide
L01AA07	Trofosfamide
L01AA08	Prednimustine
L01AA09	Bendamustine

[15] A similar database is not available for Switzerland, but the indications of drugs are unlikely to differ substantially across countries.

[16] Many drug databases contain information about drug indications, but this information is usually in text form only.

[17] Mortality data are reported in 5-years age groups. I assume that deaths in a 5-year age group occur at the midpoint of the age group. For example, I assume that deaths at age 35–39 years occurred at age 37.5. The Association of Public Health Epidemiologists in Ontario [1] uses this method.

[18] The National Institute for Cancer Epidemiology and Registration was founded in May 2007 by the Swiss Cancer Registries Network and Oncosuisse with the contribution of the University of Zurich.

of the table (lines 4–6) are of models in which the age threshold for measuring premature mortality is age 65. For each age threshold, estimates based on three alternative assumed lags (5, 10, and 15 years) between drug registration and premature mortality are presented.[19]

The left side of line 1 of Table 1 shows the FE model estimate of the effect of cumulative NCEs registered on the log of the premature (before age 75) cancer mortality rate 5 years later. The estimate is negative and significant (p value = 0.05). It indicates that premature cancer mortality was reduced by 1.2 % by an additional drug registered at least 5 years earlier. The right side of line 1 shows that the magnitude of the corresponding LD model estimate is 48 % larger; this is consistent with the hypothesis that the long-run (12-years) change in the number of drugs used to treat a condition can be measured more reliably than the number of drugs used to treat a condition in a particular year. This estimate is just slightly less significant (p value = 0.06).

In line 2, the assumed lag between cumulative NCE launches and premature mortality is 10 years. The FE estimate of β_{10} is 36 % larger than the FE estimate of β_5, and the LD estimate of β_{10} is 73 % larger than the LD estimate of β_5. As discussed above, since mean utilization of new drugs is much lower than mean utilization of older drugs, a more recent drug registration may have a smaller marginal effect on premature mortality than an earlier drug registration even if the average quality of newer drugs is higher. The LD estimate of β_{10} indicates that premature cancer mortality was reduced by 3.1 % by an additional drug registered at least 10 years earlier.

In line 3, the assumed lag between cumulative NCE launches and premature mortality is 15 years. The FE estimate of β_{15} is 33 % larger than the FE estimate of β_{10}: the LD estimate of β_{15} is approximately equal to the LD estimate of β_{10}. Both estimates are highly significant (p value <0.01). Figure 8 depicts the correlation across 13 cancer sites between the 1995–2012 log change in the premature (before age 75) mortality rate and the number of NCEs registered during 1980–1997 (i.e., the increase in cumulative NCEs registered until 15 years before).[20] The number of NCEs registered during 1980–1997 explains 63 % of the variation across cancer sites in the 1995–2012 log change in the premature (before age 75) mortality rate.

As shown in lines 4–6 of Table 1, the estimates of models in which the age threshold for measuring premature mortality is age 65 are qualitatively similar to the estimates of models in which the age threshold for measuring premature mortality is age 75.

Overall, the estimates in Table 1 indicate that premature cancer mortality before ages 75 and 65 is significantly inversely related to the cumulative number of NCEs registered 5, 10, and 15 years earlier (controlling for the number of people diagnosed and mean age at diagnosis); that LD estimates of the effect of NCE registrations are considerably larger than FE estimates (consistent with the presence of measurement error in the regressor); and that the marginal effect of more recently registered (and less frequently used) NCEs is smaller than the marginal effect of older NCEs.

As discussed earlier, premature mortality from a disease may depend on the number of chemical (or pharmacological) subgroups that have previously been developed to treat the disease rather than, or in addition to, the number of chemical substances (drugs) that have previously been developed to treat the disease. I investigated this possibility by estimating LD models with a 15-years lag in which ($CUM\_SUBGROUP_{s,1997} - CUM\_SUBGROUP_{s,1980}$) was included in addition to ($CUM\_NCE_{s,1997} - CUM\_NCE_{s,1980}$). In models of both premature mortality before age 75 and premature mortality before age 65, only the coefficients on ($CUM\_NCE_{s,1997} - CUM\_NCE_{s,1980}$) were significant. That finding suggests that drugs (chemical substances) within the same class (chemical subgroup) are not "therapeutically equivalent",[21] i.e., they do not have essentially the same effect in the treatment of a disease or condition.

Discussion

Now I will use the estimates presented in Table 1 to calculate the number of life-years gained in 2012 from pharmaceutical innovation and drug expenditure per life-year gained. These calculations are shown in Table 2. Line 1 shows the premature (before ages 75 and 65) mortality rates of all cancers combined in 2012. The estimates imply that, in the absence of previous pharmaceutical innovation, these premature mortality rates would have been higher than they actually were. On the other hand, 2012 pharmaceutical expenditure would have been lower in the absence of previous pharmaceutical innovation. I will

[19] Estimates of coefficients based on zero lag between drug registration and premature mortality ($k = 0$) were never statistically significant. This is not surprising, since as discussed above new drugs diffuse gradually—they aren't used widely until years after commercialization.

[20] Figure 8 depicts a simple correlation; controlling for the long-run change in the incidence rate and mean age at diagnosis has virtually no effect on this correlation. Neither of those variables is significant in any of the LD models.

[21] According to one medical dictionary, drugs that have "essentially the same effect in the treatment of a disease or condition" are therapeutically equivalent. Drugs that are therapeutically equivalent may or may not be chemically equivalent, bioequivalent, or generically equivalent. http://medical-dictionary.thefreedictionary.com/therapeutic+equivalent.

Table 1 Estimates of CUM_NCE coefficients from fixed-effects and long-difference models of premature cancer mortality

Line	Parameter	Fixed-effects model (Eq. 1); n = 234				Long-difference model (Eq. 4); n = 13			
		Estimate	Standard error	Z	Pr > |Z|	Estimate	Standard error	t value	Pr > |t|
A. Dependent variable = $\ln(YPLL75_{s,t})$; weight = $((\Sigma_t\ YPLL75_{s,t})/18)$									
1	β_5	−0.012	0.006	−1.98	0.048	−0.018	0.008	−2.14	0.061
2	β_{10}	−0.017	0.004	−3.95	<0.0001	−0.031	0.010	−3.01	0.015
3	β_{15}	−0.022	0.005	−4.46	<0.0001	−0.029	0.007	−4.02	0.003
B. Dependent variable = $\ln(YPLL65_{s,t})$; weight = $((\Sigma_t\ YPLL65_{s,t})/18)$									
4	β_5	−0.015	0.007	−2.05	0.040	−0.020	0.009	−2.25	0.051
5	β_{10}	−0.019	0.005	−3.44	0.001	−0.033	0.012	−2.85	0.019
6	β_{15}	−0.025	0.006	−3.99	<0.0001	−0.036	0.007	−5.02	0.001

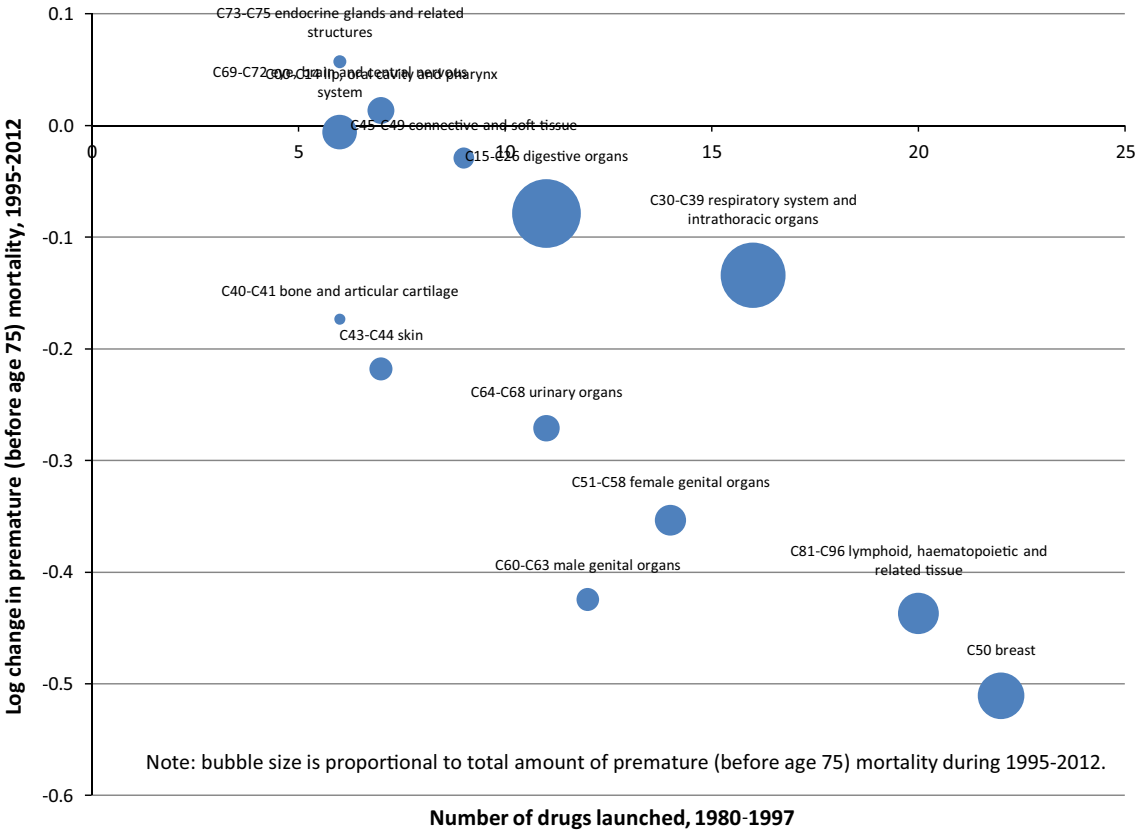

Fig. 8 Relationship across cancer sites between number of drugs launched, 1980–1997, and log change in premature mortality, 1995–2012

calculate 12 (=2 × 3 × 2) different estimates of life-years gained and their average cost, based on 2 estimation methods (FE and LD), 3 lags (5, 10, and 15 years), and 2 age thresholds (75 and 65).

As shown in line 4, the mean 1997–2012 increase in the cumulative number of drugs registered 5, 10, and 15 years earlier was 9.2, 11.8, and 11.3, respectively. As shown in line 6, the log change in premature mortality due to the increase in the cumulative number of drugs registered is $\beta_k \times \Delta CUM\_NCE_k$. For example, the LD estimate of $\beta_5 \times \Delta CUM\_NCE_5$ (=−0.164) implies that the 2012 mortality rate before age 75 would have been 18 % (=exp(0.164) − 1) higher if ΔCUM_NCE_5 had been equal to zero: the mortality rate would have been 1513 rather than its actual value of 1284. As shown in line 7, that implies that 17,092 [=(1513 − 1284) × 7.5] life-years before age 75 were gained in 2012 due to pharmaceutical innovation during 1990–2007. The LD estimates of the number of life-years before age 75

Table 2 Calculation of number of life-years gained in 2012 from pharmaceutical innovation and of drug expenditure per life-year gained

Line			Before age 75			Before age 65		
1	2012 premature cancer mortality rate per 100,000 population (RATE)		1284			540		
2	2012 population (POP)		7,471,495			6,724,518		
3	Lag (number of years) from drug registration to premature mortality (k)		5	10	15	5	10	15
4	Mean 1997–2012 increase in cumulative number of drugs registered k years earlier (ΔCUM_NCE$_k$)		9.2	11.8	11.3	9.2	11.8	11.3
5	β_k (from Table 1)	FE est.	−0.012	−0.017	−0.022	−0.015	−0.019	−0.025
		LD est.	−0.018	−0.031	−0.029	−0.020	−0.033	−0.036
6	$\beta_k \times \Delta$CUM_NCE	FE est.	−0.111	−0.195	−0.249	−0.135	−0.222	−0.286
		LD est.	−0.164	−0.368	−0.330	−0.184	−0.390	−0.404
7	Reduction in life-years lost due to pharmaceutical innovation: GAIN = [exp($-\beta_k \times \Delta$CUM_NCE$_k$) − 1] × RATE × (POP/100,000)	FE est.	11,238	20,711	27,099	5,273	9,012	12,037
		LD est.	17,092	42,688	37,535	7,357	17,327	18,117
8	Estimated expenditure (in thousands) in 2012 on drugs used to treat cancer registered during the period 1995−k to 2012−k (COST)		$362,831	$226,185	$120,804	$210,960	$131,510	$70,239
9	Cost per life-year gained (=COST/GAIN)	FE est.	$32,287	$10,921	$4,458	$40,010	$14,593	$5,835
		LD est.	$21,228	$5,299	$3,218	$28,673	$7,590	$3,877

gained from pharmaceutical innovation during 1985–2002 and 1980–1997 are more than twice as great.[22]

Line 8 of Table 2 shows estimates of expenditure in 2012 on drugs used to treat cancer that were registered during the period 1995 − k to 2012 − k (k = 5, 10, 15). Data from IMS Health were used to estimate 2012 expenditure on each of the molecules listed in Appendix Table 3.[23] Our figures are likely to overstate expenditure on drugs used to treat cancer, for two reasons. First, some of these molecules [especially those not in anatomical main group L (antineoplastic and immunomodulating agents)] are used to treat diseases other than cancer. Second, the IMS data do not account for any rebates paid by drug manufacturers to payers, although according to pharmaceutical industry executives rebates play a much smaller role in Switzerland than they do in some other countries (e.g., the USA).

The IMS Health data indicate expenditure by or on behalf of patients of all ages. Data from the National Institute for Cancer Epidemiology and Registration indicate that 70 % of patients diagnosed with cancer are diagnosed before the age of 75, and 41 % are diagnosed before the age of 65. I assumed that 70 % of 2012 expenditure on drugs used to treat cancer was for patients below age 75 and that 41 % of 2012 expenditure on drugs used to treat cancer was for patients below age 65. Since patients diagnosed before age 75 (for example) may continue to incur drug expenditure after age 75, these assumptions are also likely to be conservative, i.e., to overstate expenditure on drugs used to treat cancer on patients below age 75.

Line 9 of Table 2 shows estimates of the cost per life-year gained from previous pharmaceutical innovation. The FE estimates of the cost per life-year gained before ages 75 and 65 in 2012 from drugs launched during 1990–2007 are $32,287 and $40,010, respectively. However, as McKinnish [12] observed, "if the independent variable is an imprecise measure of the relevant factor, coefficient estimates from [FE] models can be severely attenuated towards zero". Hence, the FE estimates may well understate the number of life-years gained, and we may also be overestimating the cost. The LD estimates of the cost per life-year gained before ages 75 and 65 in 2012 from drugs launched during 1990–2007, which are likely to be less

[22] Although the percentage reductions in premature mortality due to pharmaceutical innovation are slightly larger before age 65 than they are before age 75, the (absolute) reduction in life-years lost before age 65 is considerably smaller, primarily due to the lower mortality rate (540 vs. 1284) and also to the smaller population.

[23] 2012 expenditure on the molecules listed in Appendix Table 3, by period of registration, are as follows:

Period of registration	2012 expenditure (in thousands)
1990–2007	$518,330
1985–2002	$323,121
1980–1997	$172,577

attenuated towards zero, are at least 28 % lower: $21,228 and $28,673, respectively. Moreover, the LD estimates indicate that the cost per life-year before age 75 gained from drugs launched during 1985–2002 and 1980–1997 were considerably lower: $5299 and $3218, respectively.[24]

Hirth et al. [6] performed a search of the value-of-life literature and identified 41 estimates of the value of life from 37 articles.[25] From estimates of the value of life, they calculated estimates of the value (in 1997 dollars) of a quality-adjusted life-year (QALY).[26] Four types of methods were used to produce those estimates: revealed preference/job risk, contingent valuation, revealed preference/non-occupational safety, and human capital. Median implied values (in 1997 and 2012 dollars[27]) of a QALY estimated in those studies are shown in the following table.

Study method	Number of studies	Median value of a QALY	
		1997 dollars	2012 dollars
Revealed preference/job risk	19	$428,286	$612,449
Contingent valuation	8	$161,305	$230,666
Revealed preference/non-occupational safety	8	$93,402	$133,565
Human capital	6	$24,777	$35,431

The LD estimates in line 9 of Table 2 of the cost per life-year gained before ages 75 and 65 in 2012 from drugs launched during 1990–2007 ($21,228 and $28,673, respectively) are lower than the median value in 2012 dollars of a QALY obtained from human capital studies ($35,431). Moreover, the median value of a QALY implied by other study methods was 3.8–17.3 times as high as the median value implied by human capital studies.

Summary and conclusions

The premature cancer mortality rate has been declining in Switzerland, but there has been considerable variation in the rate of decline across cancer sites. I analyzed the effect that pharmaceutical innovation has had on premature cancer mortality in Switzerland during the period 1995–2012, by investigating whether the cancer sites that experienced more pharmaceutical innovation had larger declines in premature mortality, controlling for the number of people diagnosed and mean age at diagnosis.

Premature cancer mortality before ages 75 and 65 is significantly inversely related to the cumulative number of NCEs registered 5, 10, and 15 years earlier. The number of NCEs registered during 1980–1997 explains 63 % of the variation across cancer sites in the 1995–2012 log change in the premature (before age 75) mortality rate.

Controlling for the cumulative number of drugs, the cumulative number of chemical subgroups does not have a statistically significant effect on premature mortality. This suggests that drugs (chemical substances) within the same class (chemical subgroup) are not "therapeutically equivalent".

Over 17,000 life-years before age 75 were gained in 2012 due to drugs registered during 1990–2007. The number of life-years before age 75 gained from drugs registered during two earlier periods (1985–2002 and 1980–1997) were more than twice as great. Since mean utilization of new drugs is much lower than mean utilization of older drugs, more recent drug registrations may have a smaller effect on premature mortality than earlier drug registrations even if the average quality of newer drugs is higher.

Estimates of the cost per life-year gained before ages 75 and 65 in 2012 from drugs launched during 1990–2007 are $21,228 and $28,673, respectively. These figures are below even the lowest estimates from the value-of-life literature of the value of a QALY. The estimates indicate that the cost per life-year before age 75 gained from drugs launched during earlier periods (1985–2002 and 1980–1997) were considerably lower: $5299 and $3218, respectively.

The largest reductions in premature mortality occur at least a decade after drugs are registered, when their utilization increases significantly. This suggests that if Switzerland is to obtain substantial additional reductions in premature cancer mortality in the future (a decade or more from now) at a modest cost, pharmaceutical innovation (registration of new drugs) is needed today.

Appendix

See Tables 3 and 4.

[24] The cost per life-year before age 65 gained from drugs launched during 1985–2002 and 1980–1997 were $7590 and $3877, respectively.

[25] Twenty-eight of the reviewed articles used US data; the remaining articles used data from the UK (4), Canada (3), France (1), and Denmark (1). National origin did not significantly affect the values.

[26] Lichtenberg [8] demonstrated that, although the health of cancer patients is less than perfect, the number of QALYs gained from pharmaceutical innovation could be either greater than or less than the number of life-years gained.

[27] The US Consumer Price Index increased by 43 % between 1997 and 2012.

Table 3 Drugs (sorted by Swiss launch year) used to treat various types of cancer in Switzerland

Drug	Swiss launch year	C00–C14 lip, oral cavity, and pharynx	C15–C26 digestive organs	C30–C39 respiratory system and intrathoracic organs	C40–C41 bone and articular cartilage	C43–C44 skin	C45–C49 connective and soft tissue	C50 breast
H02AB09 hydrocortisone	1953							
L01BB02 mercaptopurine	1955							
L01AA02 chlorambucil	1957							
H02AB04 methylprednisolone	1959	x	x	x	x	x	x	x
H02AB08 triamcinolone	1959			x				
L01AA01 cyclophosphamide	1960			x			x	x
L01CA01 vinblastine	1961						x	x
L01BC02 fluorouracil	1962	x	x	x				x
H02AB01 betamethasone	1963	x	x	x	x	x	x	
D07AC01 betamethasone	1964							
L01AA03 melphalan	1964						x	x
L01BA01 methotrexate	1964			x	x		x	x
H02AB02 dexamethasone	1965	x	x	x	x	x	x	
H02AB06 prednisolone	1966							
L01DA01 dactinomycin	1966						x	
G03CA03 estradiol	1967							
L01DC01 bleomycin	1970			x			x	
G03HA01 cyproterone	1972							
L01DB02 daunorubicin	1972						x	
L01BB03 tioguanine	1973							
H05BA01 calcitonin (salmon synthetic)	1976							
L01XX11 estramustine	1977							
L01AA06 ifosfamide	1979			x	x		x	x
L01CB01 etoposide	1980			x				x
A01AB09 miconazole	1981							
L01AD02 lomustine	1981			x		x		
L02AB02 medroxyprogesterone	1981							x
L01CA03 vindesine	1982	x	x	x				x
L01CA02 vincristine	1983			x	x		x	x
L01DB07 mitoxantrone	1985							x
L01XA02 carboplatin	1986	x		x				
L01XA01 cisplatin	1987		x	x				
V03AF03 calcium folinate	1987	x	x	x	x	x	x	x

Table 3 continued

Drug	Swiss launch year	C00–C14 lip, oral cavity, and pharynx	C15–C26 digestive organs	C30–C39 respiratory system and intrathoracic organs	C40–C41 bone and articular cartilage	C43–C44 skin	C45–C49 connective and soft tissue	C50 breast
B01AB04 dalteparin	1988	x	x	x	x	x	x	x
B03XA01 erythropoietin	1988	x	x	x	x	x	x	x
H01CB02 octreotide	1988		x					
J02AC01 fluconazole	1989	x	x	x	x	x	x	x
L01DB01 doxorubicin	1989		x	x	x		x	x
L01DB03 epirubicin	1990		x	x			x	x
L02AE03 goserelin	1990							x
V09GA01 technetium Tc-99M sestamibi	1991							x
L01DB06 idarubicin	1992							
L01CD01 paclitaxel	1993			x			x	x
L01XX01 amsacrine	1993							
L02AE02 leuprorelin	1993							x
M05BA03 pamidronic acid	1993							x
L01XX14 tretinoin	1994							
L02AE01 buserelin	1994							
L03AX03 BCG vaccine	1994							
V10XA01 sodium iodide (^{131}I)	1994							
J06BA02 immunoglobulins, normal human, for intravascular adm	1995							
L01BB05 fludarabine	1995							
L01CA04 vinorelbine	1995			x				x
L01XX05 hydroxycarbamide	1995							
L02AE04 triptorelin	1995							
L02BB03 bicalutamide	1995							
L03AB04 interferon alfa-2a	1995					x	x	
L01CD02 docetaxel	1996	x	x	x				x
L01XX17 topotecan	1996			x				
L02BA02 toremifene	1996							x
L02BG03 anastrozole	1996							x
V03AF05 amifostine	1996							
L01BC05 gemcitabine	1997		x	x				x
L01XC02 rituximab	1997							
L02BG04 letrozole	1997							x
L03AB05 interferon alfa-2b	1997					x		

Table 3 continued

Drug	Swiss launch year	C00–C14 lip, oral cavity, and pharynx	C15–C26 digestive organs	C30–C39 respiratory system and intrathoracic organs	C40–C41 bone and articular cartilage	C43–C44 skin	C45–C49 connective and soft tissue	C50 breast
M05BA06 ibandronic acid	1997							x
L01BA03 raltitrexed	1998		x					
L01BB04 cladribine	1998							
L01BC06 capecitabine	1998		x					x
L01XX19 irinotecan	1998		x					
D06BB10 imiquimod	1999					x		
L01AX03 temozolomide	1999							
L01BC01 cytarabine	1999							
L01XC03 trastuzumab	1999		x					x
L02BG06 exemestane	1999							x
L01XA03 oxaliplatin	2000		x					
L03AX11 tasonermin	2000						x	
M05BA08 zoledronic acid	2000	x	x	x	x	x	x	x
L01XC04 alemtuzumab	2001							
L01XE01 imatinib	2001					x		
L02BB01 flutamide	2001							
L01XC06 cetuximab	2003		x				x	
L01XD03 methyl aminolevulinate	2003					x		
H05BX01 cinacalcet	2004							
L01AB01 busulfan	2004							
L01AX04 dacarbazine	2004					x	x	
L01XC07 bevacizumab	2004		x	x				x
L01XE02 gefitinib	2004			x				
L02BA03 fulvestrant	2004							x
V10XX02 Ibritumomab tiuxetan (^{90}Y)	2004							
B03XA02 darbepoetin alfa	2005	x	x	x	x	x	x	x
J06BA01 immunoglobulins, normal human, for extravascular adm.	2005							
L01BA04 pemetrexed	2005			x			x	
L01XE03 erlotinib	2005		x	x				
L01XX32 bortezomib	2005							
J07BM01 papillomavirus (human types 6, 11, 16, 18)	2006							
L01XE04 sunitinib	2006		x					
L01XE05 sorafenib	2006		x					

Table 3 continued

Drug	Swiss launch year	C00–C14 lip, oral cavity, and pharynx	C15–C26 digestive organs	C30–C39 respiratory system and intrathoracic organs	C40–C41 bone and articular cartilage	C43–C44 skin	C45–C49 connective and soft tissue	C50 breast
H01AB01 thyrotropin	2007							
L01BB07 nelarabine	2007							
L01XE06 dasatinib	2007							
L01XE07 lapatinib	2007							x
L01XE08 nilotinib	2007							
L04AX04 lenalidomide	2007							
L01XB01 procarbazine	2008			x				
L01XC08 panitumumab	2008		x					
L01XE09 temsirolimus	2008							
L01AA09 bendamustine	2009							x
L01CX01 trabectedin	2009						x	
L01XX23 mitotane	2009							
J07BM02 papillomavirus (human types 16, 18)	2010							
L01XE11 pazopanib	2010							
V09IX06 sodium fluoride ($_{18}$F)	2010			x				x
L01XC10 Ofatumumab	2011							
L01XC11 ipilimumab	2011					x		
L01XX41 eribulin	2011							x
L02BX03 abiraterone	2011							

Drug	C51–C58 female genital organs	C60–C63 male genital organs	C64–C68 urinary organs	C69–C72 eye, brain, and central nervous system	C73–C75 endocrine glands and related structures	C76–C80 secondary and ill-defined	C81–C96 stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
H02AB09 hydrocortisone				x		x	
L01BB02 mercaptopurine							x
L01AA02 chlorambucil							x
H02AB04 methylprednisolone	x	x	x	x	x	x	x
H02AB08 triamcinolone						x	
L01AA01 cyclophosphamide	x	x	x	x	x	x	x
L01CA01 vinblastine	x	x	x				x
L01BC02 fluorouracil	x					x	
H02AB01 betamethasone				x		x	x
D07AC01 betamethasone							x
L01AA03 melphalan	x			x	x		x

Table 3 continued

Drug	C51–C58 female genital organs	C60–C63 male genital organs	C64–C68 urinary organs	C69–C72 eye, brain, and central nervous system	C73–C75 endocrine glands and related structures	C76–C80 secondary and ill-defined	C81–C96 stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
L01BA01 methotrexate	x		x	x		x	x
H02AB02 dexamethasone							x
H02AB06 prednisolone				x		x	
L01DA01 dactinomycin	x	x	x				
G03CA03 estradiol		x					
L01DC01 bleomycin	x	x				x	x
G03HA01 cyproterone		x					
L01DB02 daunorubicin							x
L01BB03 tioguanine							x
H05BA01 calcitonin (salmon synthetic)						x	x
L01XX11 estramustine		x					
L01AA06 ifosfamide	x	x				x	x
L01CB01 etoposide	x	x				x	x
A01AB09 miconazole						x	
L01AD02 lomustine				x		x	x
L02AB02 medroxyprogesterone	x						
L01CA03 vindesine						x	x
L01CA02 vincristine	x		x	x	x	x	x
L01DB07 mitoxantrone		x					x
L01XA02 carboplatin	x					x	
L01XA01 cisplatin	x	x	x				
V03AF03 calcium folinate	x	x	x	x	x	x	x
B01AB04 dalteparin	x	x	x	x	x	x	x
B03XA01 erythropoietin	x	x	x	x	x	x	x
H01CB02 octreotide						x	
J02AC01 fluconazole	x	x	x	x	x	x	x
L01DB01 doxorubicin	x		x				x
L01DB03 epirubicin	x		x			x	x
L02AE03 goserelin		x					
V09GA01 technetium Tc-99M sestamibi							
L01DB06 idarubicin							x
L01CD01 paclitaxel	x					x	

Table 3 continued

Drug	C51–C58 female genital organs	C60–C63 male genital organs	C64–C68 urinary organs	C69–C72 eye, brain, and central nervous system	C73–C75 endocrine glands and related structures	C76–C80 secondary and ill-defined	C81–C96 stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
L01XX01 amsacrine							x
L02AE02 leuprorelin		x					
M05BA03 pamidronic acid						x	x
L01XX14 tretinoin							x
L02AE01 buserelin		x					
L03AX03 BCG vaccine			x				
V10XA01 sodium iodide (^{131}I)					x		
J06BA02 immunoglobulins, normal human, for intravascular adm							x
L01BB05 fludarabine							x
L01CA04 vinorelbine						x	
L01XX05 hydroxycarbamide							x
L02AE04 triptorelin		x					
L02BB03 bicalutamide		x					
L03AB04 interferon alfa-2a			x				x
L01CD02 docetaxel		x				x	
L01XX17 topotecan	x					x	
L02BA02 toremifene							
L02BG03 anastrozole							
V03AF05 amifostine	x						
L01BC05 gemcitabine	x		x			x	
L01XC02 rituximab							x
L02BG04 letrozole							
L03AB05 interferon alfa-2b							x
M05BA06 ibandronic acid						x	
L01BA03 raltitrexed						x	
L01BB04 cladribine							x
L01BC06 capecitabine						x	
L01XX19 irinotecan						x	
D06BB10 imiquimod							
L01AX03 temozolomide				x			
L01BC01 cytarabine							x
L01XC03 trastuzumab						x	
L02BG06 exemestane							

Table 3 continued

Drug	C51–C58 female genital organs	C60–C63 male genital organs	C64–C68 urinary organs	C69–C72 eye, brain, and central nervous system	C73–C75 endocrine glands and related structures	C76–C80 secondary and ill-defined	C81–C96 stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
L01XA03 oxaliplatin						x	
L03AX11 tasonermin							
M05BA08 zoledronic acid	x	x	x	x	x	x	x
L01XC04 alemtuzumab							x
L01XE01 imatinib							x
L02BB01 flutamide		x					
L01XC06 cetuximab						x	
L01XD03 methyl aminolevulinate							
H05BX01 cinacalcet					x		
L01AB01 busulfan							x
L01AX04 dacarbazine							x
L01XC07 bevacizumab			x			x	
L01XE02 gefitinib						x	
L02BA03 fulvestrant							
V10XX02 Ibritumomab tiuxetan (^{90}Y)							x
B03XA02 darbepoetin alfa	x	x	x	x	x	x	x
J06BA01 immunoglobulins, normal human, for extravascular adm.							x
L01BA04 pemetrexed						x	
L01XE03 erlotinib						x	
L01XX32 bortezomib							x
J07BM01 papillomavirus (human types 6, 11, 16, 18)	x						
L01XE04 sunitinib							
L01XE05 sorafenib							
H01AB01 thyrotropin					x		
L01BB07 nelarabine							x
L01XE06 dasatinib							x
L01XE07 lapatinib							
L01XE08 nilotinib							x
L04AX04 lenalidomide							x
L01XB01 procarbazine				x		x	x

Table 3 continued

Drug	C51–C58 female genital organs	C60–C63 male genital organs	C64–C68 urinary organs	C69–C72 eye, brain, and central nervous system	C73–C75 endocrine glands and related structures	C76–C80 secondary and ill-defined	C81–C96 stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
L01XC08 panitumumab						x	
L01XE09 temsirolimus							x
L01AA09 bendamustine							x
L01CX01 trabectedin	x						
L01XX23 mitotane					x		
J07BM02 papillomavirus (human types 16, 18)	x						
L01XE11 pazopanib			x				
V09IX06 sodium fluoride (^{18}F)		x				x	
L01XC10 Ofatumumab							x
L01XC11 ipilimumab							
L01XX41 eribulin							
L02BX03 abiraterone		x					

Table 4 Premature cancer mortality and cancer incidence, by cancer site, Switzerland, 1995 and 2012

ICD-10 block	Year	Number of years of potential life lost before		Number of new cases diagnosed before	
		Age 75	Age 65	Age 75	Age 65
C00–C14 lip, oral cavity and pharynx	1995	3523	1585	720	534
	2012	4060	1420	886	558
C15–C26 digestive organs	1995	25,268	9543	3941	1963
	2012	26,555	9410	4660	2465
C30–C39 respiratory system and intrathoracic organs	1995	22,140	8350	2547	1391
	2012	22,020	7133	3036	1531
C40–C41 bone and articular cartilage	1995	855	590	57	42
	2012	818	580	85	71
C43–C44 skin	1995	2928	1518	979	730
	2012	2678	1158	1927	1334
C45–C49 connective and soft tissue	1995	2225	1205	141	93
	2012	2458	1140	168	109
C50 breast	1995	14,270	6673	3342	2369
	2012	9738	4065	4480	3048
C51–C58 female genital organs	1995	5945	2663	1317	828
	2012	4748	1903	1283	784
C60–C63 male genital organs	1995	3270	885	2447	937
	2012	2433	525	4955	2407
C64–C68 urinary organs	1995	4230	1383	1250	628
	2012	3668	1268	1221	575
C69–C72 eye, brain and central nervous system	1995	5648	3215	378	276
	2012	6385	3350	512	350
C73–C75 endocrine glands and related structures	1995	625	335	321	239
	2012	753	328	623	540
C81–C96 lymphoid, hematopoietic and related tissue	1995	10,485	5318	1758	1118
	2012	7703	3385	2026	1242

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